Particulate Emissions from Diesel-Fueled Engines

I. Physical and Chemical Properties

Diesel exhaust is a complex mixture of thousands of gases, vapors, and fine particles. At least 40 components are listed by the Air Resources Board (ARB) as toxic air contaminants (see Table 1).

Table 1 - Toxic Air Contaminants Found in Diesel Exhaust

Acetaldehyde	Chlorobenzene	Methanol
Acrolein	Chromium compounds	Methyl ethyl ketone
Aniline	Cobalt compounds	Naphthalene
Antimony compounds	Cresol	Nickel
Arsenic	Cyanide compounds	4-Nitrobiphenyl
Benzene	Dibenzofuran	Phenol
Beryllium compounds	Dibutylphthalate	Phosphorus
Biphenyl	Ethyl benzene	*POM (including PAHs)
bis [2-Ethylhexyl]phthalate	Formaldehyde	Propionaldehyde
1,3-Butadiene	Hexane	Selenium compounds
Cadmium	Lead compounds	Styrene
Chlorinated dioxins and dibenzofurans	Manganese compounds	Toluene
Chlorine	Mercury compounds	Xylene isomers & mixtures

* Polycyclic Organic Matter (including Polycyclic Aromatic Hydrocarbons)

Particulate emissions from diesel-fueled engines (hereinafter referred to as diesel exhaust particulate matter or DEPM) was identified by the Air Resources Board as a Toxic Air Contaminant (TAC) in 1998. Typical diesel exhaust particles have mass-median aerodynamic diameters ranging from 0.1 to 0.25 micrometers (µm) (Groblicki and Begeman, 1979; Dolan et al., 1980; NRC, 1982; Williams, 1982). More than 90 percent of the particles are smaller than 1 µm (Pierson et al., 1983; Cal/EPA, 1998), and are mainly aggregates of spherical elemental carbon particles coated with organic and inorganic substances. The particles have a sponge-like structure and large surface area which attracts compounds of low volatility to the inside or surface of the particles. The primary organic compounds associated with the particles include aliphatic hydrocarbons, polycyclic aromatic hydrocarbons (PAHs), and PAH-derivatives (Zielinska, 1990). Methylated PAHs appear to be the most abundant PAH derivatives, and more than 50 nitro-PAHs have been identified in diesel exhaust (Cal/EPA, 1998; Part

A, Appendix III). Limited data indicate PAHs and PAH derivatives are about 1% by weight of diesel exhaust particles (CE-CERT, 1997).

II. Overview

There are several lines of evidence indicating that infants and children may be disproportionately affected by diesel exhaust particulate. This includes direct evidence, such as the enhancement of allergic response and some of the truck-traffic studies evaluating respiratory health, and indirect evidence, such as health effects associated with particulate matter.

- Diesel exhaust particulate matter (DEPM) enhances allergic responses in the nasal and airway epithelium. DEPM has been reported to facilitate the development of new allergy to aeroallergens. Accumulating evidence suggests that immunological memory and the development of an allergic phenotype are established within the first few years of life, so that exposures occurring in early childhood may determine whether a child will develop allergies or not. DEPM appears to potentiate allergic responses in susceptible individuals, though the impact of DEPM on the development of an allergic diathesis has not been established. Most childhood asthma, a condition characterized by chronic airway inflammation, is associated with allergy. Airway inflammation has been demonstrated in humans after controlled exposures to diesel exhaust and DEPM. Animal studies provide strong support for the enhancement of allergic responses, and airway inflammation seen in human studies. Experimental animals also develop airway hyperresponsiveness, the functional hallmark of asthma, after exposure to DEPM.

- Several epidemiological studies conducted in Europe have reported associations between truck traffic density (largely diesel-powered) and adverse respiratory symptoms, including atopy, in children living along busy roadways. In one study examining the relationships between general traffic density and respiratory health, children appeared to be more sensitive to traffic-related pollution (e.g., cars, trucks, and buses) than adults.

- Diesel exhaust particles contribute to ambient airborne particulate matter (PM, specifically measured as PM_{10} – particles 10 microns or smaller in mean aerodynamic diameter – and $PM_{2.5,}$ a subfraction of PM_{10}). PM_{10} and $PM_{2.5}$ have been associated in numerous studies with adverse respiratory health effects in children, including exacerbation of asthma, bronchitis, cough, and wheeze. As a constituent of PM, DEPM would be expected to contribute to PM-associated health effects, although the extent of the contribution has not been directly studied and would likely vary with concentration. To the extent that asthma is more common among children than adults and that, because age-related anatomic and physiological differences can render children's airways more quickly susceptible to obstruction, one may characterize PM-associated asthma attacks as disproportionately affecting children. In some circumstances in which DEPM constitutes a significant fraction of PM (e.g., on school buses), this observation could be extended to DEPM as well. Recent epidemiological studies have also provided some evidence that exposure to PM_{10} is associated with increased infant mortality, and DEPM may contribute to this effect.

- Diesel exhaust contains polycyclic aromatic hydrocarbons (PAHs). Immunosuppressive effects have been reported in animals as a result of PAH exposure, and have been found to be more severe and to occur at lower doses early in life, especially *in utero*. Analogous effects may also occur in exposed infants and children. In addition, human fetal exposure to PAHs results in elevated levels of PAH-DNA adducts in the neonate. In experimental animals, neonates are more sensitive to such genotoxicity than their mothers. Exposure early in life to genotoxic carcinogens, which are important constituents of diesel exhaust particles, may result in higher cancer risks than when exposure occurs later in life. This represents another mechanism by which diesel exhaust particles may disproportionately impact children. PAHs have also been associated with intrauterine growth retardation and low birth weight in animals and humans. PAHs in diesel exhaust may contribute to these effects.

- Children experience higher particle doses per lung surface area than adults in the same environmental setting (see Introduction Section III.A.1.). In addition, in young children hand-to-mouth activity results in greater consumption of household dust and dirt, which in an urban setting would be contaminated by settled traffic particulates, than occurs in adults. Thus, oral exposures to PAHs (and other constituents of diesel exhaust particles) are also higher in children than adults. Differential exposure patterns are one of the criteria evaluated to prioritize the TACs for listing under SB 25.

Key studies are discussed in Section IV below.

III. Principal Sources of Exposure

Diesel exhaust PM is emitted from diesel-fueled mobile sources (on-road vehicles and off-road mobile sources), stationary area sources, and stationary point sources. Based on the 1995 emissions inventory, on-road diesel vehicles contribute approximately 58 percent (15,680 tons per year (TPY)) of California's diesel exhaust PM. Other mobile sources contribute about 37 percent (9820 TPY), and stationary area and point sources contribute the remaining amount (5% or 1400 TPY). Stationary area sources of diesel exhaust include shipyards, warehouses, heavy equipment repair yards, and oil and gas production operations where exhaust emissions result from multiple locations within the site (Cal/EPA, 1998). The primary stationary sources that have reported emissions of diesel exhaust are heavy construction (except highway), electrical services, and crude petroleum and natural gas extraction (Cal/EPA, 1998).

The total emissions of DEPM from stationary sources in California reporting under the Air Toxics Hot Spots program are estimated to be at least 31,000 pounds per year (ARB, 1997).

Emissions of DEPM from on-road mobile sources in California are expected to decline by approximately 50 percent from 1990 until about 2010 as a result of mobile source standards and regulations adopted by the ARB through 1998. The expected reduction is mainly due to diesel vehicle emission and fuel regulations, even though both the number and vehicle miles traveled (VMT) of heavy-duty trucks are expected to increase during this period (Cal/EPA, 1998). Additional efforts to reduce

DEPM emissions include the replacement of diesel-powered heavy- and medium-duty vehicles with clean-fuel alternatives (such as those using methanol or compressed natural gas), and the use of particle traps and other pollution reduction technologies on new and existing diesel engines. In September 2000, ARB approved a Risk Reduction Plan to Reduce Particulate Matter Emissions from Diesel-fueled Engines and Vehicles (Diesel RRP). The Diesel RRP includes developing regulations that will substantially reduce emissions from diesel-fueled engines.

The ARB has conducted a preliminary estimation of diesel exhaust concentrations for California's 15 air basins using a PM-based exposure method. This method used the ARB emissions inventory's database for $PM_{10,}$ ambient PM_{10} monitoring network data, and the results from several studies, in which chemical speciation of ambient data was performed, along with receptor modeling techniques, to estimate statewide outdoor concentrations of diesel exhaust PM_{10}. The 1995 outdoor statewide population-weighted average diesel exhaust PM concentration is estimated to be 2.2 micrograms per cubic meter ($\mu g/m^3$). The basin-wide average diesel exhaust PM estimates ranged from 0.1 (in the Great Basin Valley) to 2.7 $\mu g/m^3$ (in the South Coast Air Basin) (Cal/EPA, 1998). Estimates for the year 2000 are slightly lower, ranging from 0.1 $\mu g/m^3$ in the Great Basin to 2.4 $\mu g/m^3$ in the South Coast basin, on average. These statewide or basin-wide averages underestimate exposures on a smaller scale near sources of diesel exhaust emissions. For example, the ARB measured DEPM next to a freeway, reporting up to 10 $\mu g/m^3$ five meters from the freeway fence line (Cal/EPA, 1998). In addition, ARB reports a range of 3.3 to 22.9 $\mu g/m^3$ of black carbon soot measured inside a vehicle in Los Angeles under varying driving conditions (ARB, 1998). The measure of soot was strongly influenced by the presence of diesel vehicles in front of the test vehicle. Examining the PM10 measurements taken inside the vehicle under the same driving circumstances, it appears that diesel particles, measured as soot, constitute between 10 and 30 % of the PM10 mass measured inside the vehicle.

IV. Potential for Differential Effects

Several lines of evidence suggest that DEPM has the potential to differentially impact infants and children. In particular, DEPM enhances allergic responses to aeroallergens and may facilitate the development of new allergies in susceptible individuals. This may have implications for the development and exacerbation of pediatric asthma, which is considered to be related to allergy in about 80% of cases (Pearce et al. 1998).

During the past few years substantial evidence has accumulated suggesting that the development of an allergic phenotype (atopy), which can render one susceptible to asthma, allergic rhinitis, and eczema, may be determined by exposures occurring in early childhood (Brehler et al. 1999). People who develop atopy have a genetic predisposition to produce IgE (immunoglobulin E) antibodies against inhaled or ingested environmental antigens. Whether atopy actually develops appears to depend, at least in part, on early-life exposures to certain allergens, particularly those found indoors. Development of sensitivity to aeroallergens is a complex process requiring an orchestrated coordination of antigen-presenting cells (macrophages or dendritic cells in the airways), T-lymphocytes and B-lymphocytes, which produce IgE antibodies against specific antigens. IgE-mediated hypersensitivity to aeroallergens is a key ingredient in the evolution of the chronic inflammation observed in asthma. While the role of

DEPM in the development of atopy is undefined, numerous studies suggest that DEPM exposure enhances IgE-mediated and other responses to aeroallergens in atopic individuals, including worsening symptoms of allergic rhinitis. In addition, to the extent that DEPM exposure may facilitate the development of allergic sensitization, it may enlarge the spectrum of aeroallergens that may cause symptoms in any given individual with allergic rhinitis or asthma.

DEPM is a variable component of ambient PM_{10}, which has been shown in epidemiological studies to exacerbate asthma, and is associated with elevated risk of cough, chronic bronchitis and wheeze. Traffic studies also contribute to the evidence that DEPM affects respiratory function, and one study examining impacts of traffic-related pollution on respiratory function indicates that children were impacted to a greater degree than adults in the same households. In addition, PM_{10} is associated with increased infant mortality in a number of studies, including in areas where diesel exhaust is a major component of urban PM_{10}. The lines of evidence are discussed in the following sections.

A. Summary of Key Human Studies

a) Immunological and Respiratory Effects of Diesel Exhaust PM

There is growing scientific evidence that diesel PM enhances allergic responses to pollen and other allergens. Enhancement of allergic responses in the nasal and airway epithelium may increase rates of allergic rhinitis and possibly asthma in children. Japanese researchers evaluating the prevalence of Japanese cedar allergy found that pollinosis (as manifested by symptoms of allergic rhinitis isolated to the cedar pollen season, and confirmed in individuals seeking medical care by allergy skin and blood tests) was higher among residents living near heavily trafficked roads lined with cedars than in residents living in cedar forests without traffic congestion (Ishizaki 1987). Though these results are striking, they should be considered suggestive, as the researchers didn't control for some important confounders. A number of studies indicate that DEPM can induce immunological allergic reactions as well as localized inflammatory responses in humans (Diaz-Sanchez et al., 1994, 1996, 1997, 2000; Terada et al., 1997, Takenaka et al., 1995). Diaz-Sanchez et al. (1997, 1999) found that in allergic human subjects, nasal IgE antibody response and allergic inflammation were enhanced by co-exposure to diesel particulate matter. They also demonstrated that DEPM can induce sensitization in atopic individuals to a new allergen. Both *in vivo* and *in vitro* studies exploring the mechanisms of enhanced response to allergen have been conducted. Casillas et al (1999) suggest that DEPM may enhance allergic inflammation through increased formation of reactive oxygen species by DEPM-associated PAHs engulfed by phagocytic cells. This in turn may activate intracellular signaling pathways that result in the production and secretion of biochemical messengers (chemokines and cytokines) involved in allergic inflammation. Key studies demonstrating the enhancement of allergic responses by diesel exhaust are discussed below.

(1) Intranasal instillation studies

Diaz-Sanchez et al. (1997) challenged thirteen subjects who had a positive skin test to short ragweed intranasally with ragweed (RW) pollen alone or with diesel exhaust particulate matter (DEPM) (0.3 mg). Nasal lavage fluids were examined for immunoglobulin (Ig) secreting cells, levels of various Igs and

cytokine profile. The number of IgE-secreting cells was significantly elevated in nasal washes (day 4) following exposure to RW alone or RW+DEPM, while the number of IgA-secreting cells was not. Challenge with RW plus DEPM significantly increased the levels of total and RW-specific IgG4 and of RW-specific IgE in nasal lavage fluids compared to RW alone. IgE represents antibodies associated with allergy, while the gene coding for IgG4 is located in close proximity to that coding for IgE; thus, changes in levels of these Igs often occur in concert. On day one, RW-specific IgE levels were 6 times higher in RW + DEPM subjects (62.7 $\pm$ 55.1 Units/ml) compared with RW alone (10.2 $\pm$ 10.2 U/ml). By day 4 the RW-specific levels were 16 times higher in the RW + DEPM subjects (up to 180 U/ml) than in the RW-alone lavage fluids (up to 12 U/ml). These differences were highly significant ($p < 0.005$ and $p < 0.001$ for days 1 and 4 post-challenge, respectively). Levels of mRNA 18 hours post-challenge for the Th-2-type cytokines IL-4, IL-5, IL-6 and for IL-10 and IL-13 were significantly greater ($p < 0.01$ to $p < 0.05$) in cells recovered from the nasal lavage fluid of those challenged with RW + DEPM relative to RW alone. ("Th-2" refers to a subset of white blood cells [lymphocytes] associated with allergic-type responses, in contrast to Th-1 lymphocytes considered to be associated with nonallergic immune responses.) The authors note that the sentinel Th-1-type cytokine interferon gamma (IFN- γ) was significantly decreased by exposure to DEPM +RW but not by RW alone. These results indicate that the activation of Th-2 cells by allergen exposure can be markedly augmented by exposure to DEPM, with striking effects in the production of antigen-specific IgE, which may in turn increase the likelihood of respiratory symptoms. In another study, these investigators found that the messenger RNA (mRNA) for pro-inflammatory cytokines in macrophages and nasal epithelial cells were significantly increased in human volunteers following intranasal instillation of diesel particles (Diaz-Sanchez et al., 1996).

Nasal challenge with DEPM induced sensitization to a neoallergen in atopic individuals (Diaz-Sanchez et al., 1999). In this study, ten atopic (i.e., allergic) subjects were administered a solution of keyhole limpet hemocyanin (KLH) or KLH + DEPM intranasally three times at two-week intervals. IgE anti-KLH antibodies were present in the nasal lavage fluids at 28 and 32 days for those administered KLH + DEPM, but not in the KLH alone group. Anti-KLH IgG4 levels in lavage fluid were higher in the KLH + DEPM group relative to the KLH group ($p < 0.01$). There was no change in IFN-γ pre-challenge and post-challenge in either group, but challenge with KLH + DEPM greatly increased the levels of IL-4 (a cytokine that has a major influence on the synthesis of IgE by B-lymphocytes) in the nasal lavage fluid, whereas there was no increase in the KLH-only group. This study demonstrates that DEPM can induce sensitization in atopic individuals to a new allergen (as measured by production of KLH-specific IgE) under conditions where administration of the allergen alone does not induce sensitization. Production of IgE antibodies in response to inhaled antigens is the hallmark of sensitization. The authors note that exposure to airborne DEPM may cause atopic individuals to become sensitized to materials to which they would not otherwise respond.

In addition, DEPM administration has been shown to potentiate allergic rhinitis symptoms in volunteers (Diaz-Sanchez et al., 2000). In this study, 11 volunteers allergic to dust mite were administered dust mite allergen intranasally to stimulate an allergic response. A single-blind, placebo-controlled cross-over study design was implemented with subjects randomly receiving 0.3 mg DEPM, 0.3 mg carbon black (CB), or saline intranasally at intervals separated by at least 6 weeks. Immediately following

DEPM, CB, or saline administration, a dust mite allergen challenge was performed and the dose necessary to obtain a pre-designated symptom score was determined. (Symptoms included sneezing, nasal itching and congestion, and rhinorrhea.) Co-administration of DEPM markedly increased the symptom scores after nasal challenge. Only about 1/5 the amount of allergen was needed to provoke the same symptom score when given with DEPM as compared with allergen alone. Carbon black co-administration with allergen did not increase the symptom score relative to saline plus allergen. In a second phase of the study, subjects were given allergen alone, allergen plus saline, allergen plus DEPM, or allergen plus CB intranasally. Histamine (a vasoactive amine associated with allergic symptoms and bronchoconstriction) in nasal lavage supernatant was measured. Higher histamine levels were measured in the supernatant of the nasal lavage fluid when DEPM was co-administered with allergen compared to allergen administration with saline or CB. In addition, the investigators showed potentiation of histamine release by DEPM extract in a murine mast cell line. This investigation demonstrates that DEPM can affect mast cells (containing pre-formed histamine) to augment immediate responses to allergen, and can elicit symptoms of allergic rhinitis in circumstances in which exposure to allergen alone would not.

(2) In vitro cell studies

In experiments *in vitro*, extracts of PAHs from DEPMs (PAH-DEPM) enhanced the production of IgE in purified human B cells prepared from blood mononuclear or tonsil cells (Takenaka et al., 1995). Terada et al. (1997) found that DEPM extracts enhanced human eosinophil adhesion to nasal epithelial cells, an event necessary for the infiltration of inflammatory cells from the circulating pool in the blood to tissues, and caused eosinophil degranulation, which plays an important role in nasal allergy. (Eosinophils are a class of white blood cells involved in allergic inflammation and asthma, as well as other conditions.) These same investigators showed that incubation of human nasal epithelial cells and mucosal microvascular endothelial cells with DEPM extract caused an increase in the expression of mRNA for the histamine-1 receptor (HR-1), and increased the amounts of the cytokines interleukin-8 (IL-8 – a chemoattractant or chemokine for neutrophils, white blood cells involved in acute inflammatory reactions) and granulocyte macrophage colony stimulating factor (GM-CSF – a growth factor promoting the development of two types of immune/inflammatory cells) in the incubation medium (Terada et al., 1999). In this study the epithelial and endothelial cells were incubated in the presence or absence of DEPM extract, 0.5 to 50 ng/ml, for 6 to 24 hours. HR-1 mRNA expression was significantly increased at 50 ng DEPM extract/ml relative to controls. Histamine-induced secretion of IL-8 and GM-CSF into the culture medium was significantly increased at 50 ng extract/ml relative to controls. The authors conclude that DEPM enhances inflammation by upregulation of the HR-1 receptor as well as increasing the production of the inflammatory cytokine IL-8 and GM-CSF.

In a similar vein, Bayram et al.(1998) observed that exposure of human bronchial epithelial cells *in vitro* results in the release of the pro-inflammatory cytokine IL-8, GM-CSF, and intercellular adhesion factor molecule-1 (ICAM-1) from these cells, which could influence the development of airway disease. The study utilized cultured bronchial cells recovered from lung cancer patients (from cancer-free areas), and exposed the cells to varying concentrations of suspended DEPM (50 to 100 µg/ml). Analysis of the cell culture medium after 24-hour incubation indicated a dose-dependent release of IL-8 ($p < 0.05$), which was significantly greater than when cells were incubated in the presence of similar concentrations of

activated charcoal or controls. Both ICAM-1 and GM-CSF were increased but only at the middle dose (50 µg/ml). The increase at the high dose or 100 g/ml DEPM (100 µg/ml DEPM) was not significant at $p < 0.05$. Upregulation of ICAM-1 has been observed in human bronchial epithelial cells in culture by others (Takizawa et al., 2000). In another in vitro study, an organic extract of DEPM was evaluated for its ability to modulate production of chemotactic cytokines (chemokines) by peripheral blood mononuclear cells from healthy human donors (Fahy et al., 1999). Polycyclic aromatic hydrocarbons extracted from DEPM were incubated with PBMC at concentrations ranging from 0.5 to 50 ng/ml up to 48 hours. Concentrations of chemokines (IL-8, RANTES [**R**egulated on **A**ctivation, **N**ormal **T**-cell **E**xpressed and **S**ecreted], and MCP-1) were quantified in the supernatant, and mRNA for the chemokines was evaluated in the cells. Dose-dependent increases in IL-8 and RANTES were observed from 2 to 48 hours; while MCP-1 decreased. The same pattern of mRNA expression (increased for IL-8 and RANTES, decreased for MCP-1) was observed in the cells measured at 24 hrs, indicating that the DEPM-PAH extracts act at the transcriptional level. The authors note that this modulation of chemokine production may favor preferential recruitment of neutrophils (by IL-8), eosinophils and memory T cells (by RANTES) but not monocytes and macrophages (by MCP-1) upon exposure to diesel exhaust.

All these studies *in vitro* support the inflammatory reactions and modulation of inflammatory cells and cytokines observed after intranasal instillation of DEPM and inhalation of whole DE, and provide some potential mechanisms by which DEPM may exacerbate allergies and asthma.

(3) Exposure to diesel exhaust via inhalation

Exposures of humans to whole diesel exhaust via inhalation have also demonstrated inflammatory responses. Salvi et al. (1999) exposed 15 healthy nonatopic volunteers to whole diesel exhaust (0.3 mg/m^3 as particulate) or air on two different occasions for one hour with 15 minute exercise periods. Lung function measurements including peak expiratory flow rate (PEFR), forced vital capacity (FVC), forced expiratory flow in 1 second (FEV1), and forced expiratory flow mid range (FEF25-75%) were taken immediately before and after exposures. Endobronchial biopsy, bronchial wash (BW), and bronchoalveolar lavage (BAL) were also performed 6 hours after exposure. BW and BAL fluids were centrifuged and a differential cell count conducted on the pellet. The supernatant was analyzed for albumin, protein, lactate dehydrogenase (LDH), IL-8, ICAM-1, fibronectin, methylhistamine, and other indicators of injury. There were no differences in lung function measurements between DE-exposed and control subjects. However, a marked inflammatory response was observed in DE-exposed subjects manifested as increased numbers of neutrophils in the BW, and increases in B- lymphocytes, methylhistamine levels, and fibronectin in the BAL, as well as increases in the number of neutrophils in the submucosa (3-fold; $p < 0.003$) and epithelium (4-fold, $p < 0.03$) of the bronchial biopsies. There were also statistically significant increases in mast cell numbers ($p < 0.002$), CD4+ and CD8+ cells (T lymphocytes) ($p < 0.04$) in the submucosa and/or epithelium of the bronchi of DE-exposed subjects. Marked increases in immunostaining for the endothelial adhesion molecules ICAM-1 and VCAM-1, as well as increased numbers of cells expressing ligand for ICAM-1, VCAM-1 ($p < 0.007$ and $p < 0.03$, respectively) and LFA-1 (a leukocyte adhesion molecule) ($p < 0.001$) were observed in the epithelium and submucosa. These adhesion molecules facilitate transfer of circulating inflammatory cells into

tissues. Peripheral blood samples 6 hr after DE exposure showed a significant increase in neutrophils and platelets following DE exposure. This study shows clearly that diesel exhaust exposure results in an acute inflammatory response and that lung function tests, which have traditionally been used to assess responses to environmental insults such as diesel exhaust exposure, may still be normal in the presence of lung injury and inflammation. In another study by the same investigators (Rudell et al., 1999), bronchoalveolar lavage was performed on 10 healthy subjects following a 1-hour exposure to air, diesel exhaust or filtered diesel exhaust. Each subject received each exposure in random order at 3-week intervals. Differential cell counts were performed on the BAL fluid and phagocytosis was measured. As in the previous study, diesel exhaust exposure resulted in a recruitment of inflammatory cells into the airway. The particle filter did not reduce the effect observed, although it should be noted that the particle filtering efficiency was only 50%, and as such may not have been sufficient to separate effects of particles from vapor phase constituents.

Nightingale et al. (2000) also studied airway responses in healthy volunteers following a 2-hr exposure to 0.2 mg DEPM/m^3. As in the study by Salvi et al (1999), there were no measurable changes in lung function in DEPM-exposed subjects, but an inflammatory response was observed, as measured by increases in neutrophil count and myeloperoxidase levels in induced sputum and by increased exhaled CO levels (a measure of oxidative stress).

(4) Epidemiological studies – traffic-related respiratory effects

Several environmental epidemiological studies provide evidence supporting the notion that exposure to diesel exhaust may contribute to the expression of allergic disease, including asthma. Reports also suggest associations between exposure to truck traffic, which consisted largely of heavy-duty diesel trucks, and a variety of adverse respiratory outcomes, including symptoms of asthma and allergic rhinitis. These endpoints are particularly important to children's health, and the studies summarized below specifically included health evaluations of exposed children.

There are observations in children of atopic sensitization (Kramer et al., 2000), asthma and allergic rhinitis (Edwards et al. 1994, Duhme et al., 1996), decreased lung function (Wjst et al., 1993) and various chronic respiratory symptoms (van Vliet et al., 1997, Oosterlee et al., 1996) associated with increased traffic density. In the study by Duhme et al. (1996), truck traffic specifically was associated with wheezing (OR 2.47, 95% CI 1.74 – 3.52 for constant truck traffic on street of residence relative to no truck traffic) and allergic rhinitis (OR 1.96, 95% CI 1.40 – 2.76 for constant truck traffic) in children aged 12 - 15. The more recent report by Ciccone et al. (1998) also found associations of adverse respiratory health impacts in children with heavy vehicular (diesel powered) traffic. In this study, children living in metropolitan centers along streets with frequent truck traffic (in relation to no truck traffic) showed significantly increased risks for bronchiolitis (OR 1.74, 95% CI 1.09 – 2.77), pneumonia (OR 1.84, 95% CI 1.27 – 2.65) and for multiple episodes of bronchitis (OR 1.69, 95% CI 1.24 – 2.30) early in life (0-2 years). There were also increased risks of current respiratory symptoms, including wheeze and cough, in children living along streets with frequent truck traffic compared with those children living along streets with the no truck traffic.

Studies from Holland indicate that diesel particulate is associated with respiratory impacts (Brunekreef et al., 1997; van Vliet et al., 1997). These investigators not only used traffic counts, but also measured carbonaceous particulate material in indoor air in schools, and found a strong association of decreased lung function with black particle exposure and truck traffic density (Table 2). In this cross-sectional study, over 1000 children ages 7-12 years living in six areas in the Netherlands with homes located near major roadways (carrying between 80,000 and 152,000 total vehicles per day, including between about 8,100 to 17,600 trucks/day) were evaluated with respiratory questionnaires and lung function tests. Measures used to assess exposure to traffic-related pollutants included: 1) distance of the children's homes and schools from major roadways; 2) traffic density counts; 3) and indoor measurements of PM_{10} (with conversion to Black Smoke (BS), representing largely soot particles) and NO_2. Multiple linear regression was used to investigate associations between lung function and pollution measures, adjusting for age, height, weight, gender, parental respiratory symptoms, smoking in the home, pets, dampness or mold in home, ethnicity, number of persons in the home, gas cooking, gas-fired unvented heaters, and socioeconomic status (parental education). Truck traffic density was related to forced expiratory volume in 1 second (FEV1), and peak expiratory flow (PEF) for children living within 1000 m of a major roadway. Decrements in lung function were strongly associated with truck traffic density rather than with automobile traffic density. The effect of truck traffic density on FEV1 increased when the analysis was restricted to children living within 300 m of a roadway, enhancing the likelihood of a causal association. For girls, the effects were stronger than for boys. A clear dose-response relationship was observed between truck traffic density and forced expiratory volume in one second (FEV_1) in children living <300 meters from a roadway (see Figure 1 in Brunekreef et al, 1997).

Respiratory symptoms from the same cross-sectional study were reported by van Vliet et al. (1997), based on parental responses to questionnaires for 1068 children. More symptoms were reported for children living within 100 m of the roadway than for those living within 1000 m of a major roadway. BS concentrations decreased with increasing distance from the freeway. The strongest associations between pollution and respiratory symptoms were observed in girls: chronic cough and wheeze were significantly elevated for girls living within 100 m of a major roadway relative to those living between 100 and 1000 m away (OR = 2.45, 95% CI = 1.16-5.16 for chronic cough, and OR=3.05, 95% CI = 1.11-8.41 for wheeze). Van Vliet et al. (1997) also reported substantially elevated point estimates for odds ratios relating density of truck traffic and BS concentrations measured in schools to these symptoms as well as to asthma attacks, rhinitis, and bronchitis in the past year (ORs ranged from 1.93 to 4.34 in girls only, but were not statistically significant).

Table 2. Lung function decrements as percentage changes (95% CI in parentheses) in forced expiratory volume in 1 second (FEV1) and peak expiratory flow rate (PEFR) in children living near major roadways by measures of vehicle-related air pollution

Population and pollution indicator	FEV1 per 10,000 trucks	FEV1per 10 mg BS/m^3	PEFR per 10,000 trucks	PEFR per 10 mg BS/ m^3
All children living within 1000 m of roadway	-2.5 (-5.3, 0.4)	-1.2 (-3.5, 1.5)	-8.0 (-12.2, -3.6)	-2.6 (-6.7, 1.6)
All children living within 300 m of roadway	-4.1 (-7.9, -0.1)	-3.7 (-7.2, -0.2)	-7.7 (-13.4, -1.7)	-5.8 (-11.1, -0.2)
Boys living within 300 m or roadway	-1.8 (-7.5, 4.2)	1.9 (-3.8, 8.0)	-9.7 (-17.8, -0.7)	-2.5 (-11.2, 7.0)
Girls living within 300 m of roadway	-6.2 (-11.5, -0.6)	-8.3 (-13.0, -3.4)	-6.1 (-13.9, 2.4)	-7.8 (-14.7, -0.3)

Source: Brunekreef et al (1997)

Oosterlee et al. (1996) present data indicating that children may be disproportionately impacted by traffic-related pollutants. In this study, the CAR ("**C**alculation of **A**ir pollution by **R**oad traffic") model was used to estimate pollution levels for each street in the city of Haarlem, the Netherlands. The model accounts for kind of vehicles (car, bus, truck, gas-fueled, diesel-fueled), mean traffic density, emissions rates for each type of vehicle, local topography including buildings, background concentrations, and meteorology to estimate air pollution levels. Validation measures showed a mean error of 6% (SD=9%) for peak NO_2 concentrations. Respiratory symptoms in children (up to 15 yrs of age) living along streets with estimated traffic density of 10,000 to 30,000 vehicles/day (estimated NO_2 concentrations of 62 to 80 ppb) were compared to those of children living in the same neighborhoods on streets with little traffic. Symptoms were ascertained by questionnaires completed by the subjects' parents, who provided information about chronic cough, episodes of cough with phlegm, wheeze, dyspnea, attacks of dyspnea with wheeze, doctor-diagnosed asthma, medication use, allergy, school absenteeism, doctor visits, for 106 children living on busy streets and 185 "control" children. Adjusted odds ratios for girls were significant for wheeze ever, wheeze in the past year, dyspnea with wheeze ever, dyspnea with wheeze in the past year, and respiratory medication use (Table 3). In contrast to the strong effects in girls, none of the symptoms appeared elevated in boys. This is interesting and not easily explained, but consistent with reports by Brunekreef et al. (1997) and van Vliet et al. (1997). Current asthma medication use was significant for all children, boys and girls combined, living along busy streets (OR 2.2 (95% CI = 1.1-4.6)), but not for adults. The authors conclude that the apparent lack of effect

in adults relative to the children indicates a difference in susceptibility to ambient traffic related air pollution between children and adults. While this study did not directly measure DEPM, diesel exhaust is a major component of traffic-related pollution in the Netherlands, including NO_2, the pollutant modeled in this study.

Table 3. Respiratory symptoms in girls (0-15 years of age) living along busy streets (relative to girls living on streets with little traffic).

Symptom	Adjusted OR (95% CI) for girls
Wheeze-ever	4.4 (1.4-13.6)
Wheeze in past year	5.3 (1.1-25.0)
Dyspnea w/ wheeze ever	4.8 (1.3-17.7)
Dyspnea w/ wheeze in past year	15.8 (1.4-17.7)
Respiratory medication	2.9 (1.1-7.9)
Doctor diagnosed allergy	2.5 (0.7-9.2)

Adjusted for age, maternal education, passive smoking, presence of unvented hot water heater, heating type, home humidity, pets, and crowding.
Source: Oosterlee et al., 1996.

b) Epidemiological studies - General Ambient PM_{10} Effects

Diesel exhaust particulate contributes to ambient particulate matter 10 μm in diameter or less (PM_{10}), especially in areas with heavy traffic. The extent of the contribution of diesel exhaust particulate to PM_{10} health effects has not been directly studied. However, health effects of PM_{10} may be, in part, attributable to the diesel exhaust particulate component. Exposure to PM_{10} in ambient air (to which diesel exhaust is a significant contributor in many urban areas) has been associated with a number of adverse effects on the respiratory system, particularly cough, phlegm and other symptoms of irritation, and decline in lung function. Reported adverse effects include both measures of morbidity (symptoms, increased hospital admissions), and increased mortality. These effects are particularly seen for asthmatics and those with other existing respiratory or cardiovascular disease, and the elderly (Thurston, 2000 as included in Cal/EPA, 2000). Although the contribution of diesel exhaust particulate to the statewide average PM_{10} is relatively small in California (5% or so), it is a more significant portion of PM_{10} and $PM_{2.5}$ in urban locations. In addition, in some cities outside the U.S. that have been studied for effects of PM_{10}, diesel is the major contributor to total PM_{10}. Ostro et al. (1996), in a mortality-PM time-series study in Santiago, Chile, cites Sandoval et al. (1985) which indicates approximately 74% of the PM_{10} in Santiago is from diesel sources. Diesel vehicles account for about 87% of black smoke emissions in London (QUARG, 1993). Effects of PM_{10} are quantitatively similar across different cities

throughout the world with varying constituents of PM_{10}. Thus, cardiovascular and respiratory morbidity and mortality that have been repeatedly linked to ambient PM appear to be an effect of small particles in general. There is no reason to expect a priori that particles from a diesel-fueled source would be selectively less toxic than those from other combustion sources which contribute to ambient PM. There certainly is not a protective effect for morbidity or mortality in the cities where diesel exhaust contributes a substantial portion of the PM_{10}.

(1) Effects of ambient PM_{10} pollution on infants and children

Numerous investigators have reported that respiratory symptoms in children can be exacerbated by exposure to airborne particles and sulfates. These effects have greater health implications in children with asthma, and can lead to an increased incidence of asthma attacks. Since the prevalence of asthma is higher among children than among adults (CDC, 1996a,b), PM-related exacerbations may put proportionately more children at higher risk. Diesel exhaust particles contribute to ambient air $PM_{10,}$ particularly in urban areas with heavy vehicular traffic. In the Thurston et al. (1997) study of children with asthma at a summer camp, prescription medication use, as prescribed in physician-verified cases of asthma exacerbation, was a metric of severe air pollution effects associated with sulfate (a measure of particle pollution). Ostro et al. (1995) in a paper published in a peer-reviewed proceedings, found significant associations between PM_{10} and asthma symptoms in 7-12 year old Los Angeles residents. This finding was confirmed and strengthened in a subsequent study (Ostro et al., 2001). Delfino et al. (1998) found significant associations between asthma symptoms in children 9-17 years of age with both 1-hour and 8-hour PM_{10} measurements. In an earlier study, Delfino and colleagues found a significant association between PM_{10} and bronchodilator use in asthmatic children (Delfino et al. 1997). In a re-analysis of published studies, Hoek et al. (1998) noted significant reductions in peak expiratory flow rates in children associated with PM_{10} measurements. Pulmonary function has also been associated with measurements of particulate matter 5 microns or smaller in a study in school children (Linn et al., 1996). In a large study in 12 Southern California communities, asthma, bronchitis, cough, wheeze and lung function decrements were associated with PM_{10} pollution, as was deficits in lung function growth in children, though because of pollutant covariation, these effects could not be ascribed exclusively to PM (Peters et al., 1999a,b; Gauderman et al., 2000). In any case, the published literature is replete with findings that PM air pollution can adversely affect children's respiratory health.

Burnett et al. (1994) note that the largest percent increase in hospital admissions associated with PM_{10} is in the 0-1 year old age group of children in Ontario, suggesting that infants may be especially susceptible (see also Introduction section III). Infant and child mortality has also been associated with acute exposures to PM_{10} pollution in time-series studies in Mexico (Loomis et al., 1999), Delhi (Cropper et al., 1997) and Bangkok (Ostro et al., 1998) and in a case-control study in the Czech Republic (Bobak and Leon, 1999). The time-series study design allows the investigator to account for the potential effects of other co-varying pollutants on infant and child mortality, and these studies were able to ascribe the effects to PM_{10} pollution. Other cross-sectional studies have linked infant mortality in the U.S. (Woodruff et al., 1997) and the Czech Republic (Bobak and Leon, 1992) to longer-term exposures to PM, although the influence of other pollutants in these cross-sectional studies can't be easily characterized and thus confounding may exist.

Children are also exposed to more PM per unit body weight and per lung surface area than adults by virtue of their higher breathing rates (see Section III in the Introduction). The studies showing infant and child morbidity and mortality, combined with higher doses due to higher breathing rates of children, as well as higher rates of asthma in children, indicate that children may be disproportionately impacted by PM relative to adults. This conclusion was supported by the review of our prioritization of the Criteria Air Pollutants (CAP) under SB 25 by the Air Quality Advisory Committee. Indeed, PM_{10} was determined to be the highest priority CAP for re-review of the standard (Cal/EPA, 2000).

c) Carcinogenicity

The epidemiological studies of the relationship between human exposure to diesel exhaust and lung cancer involve occupational situations that necessarily involve adults but not children, so direct evidence of differential effects on infants or children is not available from this source. There are a considerable number of studies of adult human exposure to diesel exhaust in an occupational setting and associations with cancer. Lipsett and Campleman (1999) identified 39 independent estimates of relative risk among 30 studies of diesel exhaust and lung cancer, while HEI (1995) summarized more than 35 epidemiologic studies (16 cohort and 19 case-control) of occupational exposure to diesel emissions. Meta-analyses from the existing studies support the observed association between occupational exposure to diesel exhaust and increased risk of lung cancer. These analyses also found that the relationship between occupational diesel exhaust exposure and lung cancer could not be attributed to potential confounding by cigarette smoking (Bhatia et al., 1998, HEI, 1995; Lipsett and Campleman, 1999). The available studies were reviewed in the TAC document *Health Risk Assessment For Diesel Exhaust* (OEHHA, 1998).

It has been noted in the introductory chapter of this report that cancer risks may generally be more severe when exposure occurs *in utero* or early in postnatal life. Additionally, it is known that diesel exhaust particulate contains PAHs and PAH derivatives. These are suspected of being substantial contributors to the observed carcinogenicity of diesel exhaust. In a separate section of this report, evidence is presented that benzo[*a*]pyrene and other PAHs are not only carcinogenic to adults, but present a significantly greater hazard of carcinogenicity to the fetus and to infants and children. This evidence includes data on DNA adducts following human exposure to PAHs. In addition, developmental toxicity has been observed following PAH exposure *in utero*, including reduced birth weight and dysmorphogenesis. The evidence in this case also is primarily for exposure to PAHs in tobacco smoke and ambient or indoor air pollution. Thus, the presence of PAHs in diesel exhaust poses another concern for disproportionate impacts on infants and children. The reader is referred to the summary of differential toxicity for benzo[*a*]pyrene and PAHs in this report for further details of these effects.

B. Summary of Key Animal Studies.

Animal studies support the enhancement of allergic and inflammatory responses seen in human studies. These studies provide evidence that diesel exhaust can potentiate responses to aeroallergens, which

could facilitate the exacerbation and possibly the evolution of allergic diseases, including asthma and allergic rhinitis.

a) Immunological Toxicity

Studies in mice have shown that intranasal or intraperitoneal co-administration of DEPM and allergen and inhalation of DEPM enhances IgE production in response to Japanese cedar pollen and ovalbumin (Muranaka et al., 1986; Takafuji et al., 1987; Takano et al., 1997; Miyabara et al., 1998). These studies were initially undertaken because of an increase in prevalence of allergic rhinitis caused by pollens in Japan that corresponded to an increase in the number of diesel-fueled cars in Japan, and the higher rates in polluted urban areas relative to nonpolluted areas (Muranaka et al., 1986; Takafuji et al., 1987; Miyamoto, 1997). DEPM can enhance antigen-induced airway inflammation in a mouse model (Takano et al., 1997). Male ICR mice were treated intranasally with either ovalbumin (OVA), DEPM, OVA + DEPM, or vehicle weekly over 6- or 9-week periods. Bronchoalveolar lavage (BAL) and differential cell counts of the lavage fluid, and lung histology were conducted 24 hours after the last treatment. Measurements of eosinophils, lymphocytes, and neutrophils in BAL fluid as well as in the lung tissue were conducted. In addition, the investigators quantified cytokine levels in BAL and lung tissue supernatants. OVA-specific IgE, IgG1, and IgG2a were measured. A 20-fold greater increase in the eosinophil content of BAL fluid was observed in mice instilled with OVA + DEPM relative to OVA alone. The vehicle group showed no eosinophils in the BAL fluid. DEPM co-administration also produced a 10-fold increase in neutrophils and a 4-fold increase in lymphocytes in the BAL fluid relative to OVA alone. A marked infiltration of eosinophils and lymphocytes was noted in the bronchioles and bronchi of DEPM + OVA treated mice compared to OVA or DEPM alone. Goblet (mucous-secreting) cell number in the airway epithelium was increased 13-fold in the OVA + DEPM group relative to the OVA group alone. These results were all statistically significant ($p < 0.05$ to $p < 0.001$). The Th2 cytokine IL-5, which is involved in the pathogenesis of allergic reactions through enhancement of differentiation, recruitment and activation of eosinophils, was highly elevated in BAL fluid and lung tissue supernatants of OVA + DEPM mice relative to those for OVA or DEPM alone. Antigen-specific immunoglobulins IgE, IgG1, and IgG2a were all significantly elevated in the DEPM + OVA group compared to the OVA group alone after 9 weeks of treatment. The authors note that these cellular and cytokine changes demonstrate enhanced allergic airway inflammation from exposure to DEPM, and that the co-administration of DEPM and antigen "established the fundamental traits of asthma, including eosinophilic airway inflammation, airway hyperresponsiveness, and mucus hypersecretion…"

Exposure of OVA-sensitized C3H/HeN mice via inhalation (2-3 mg/m^3) for five weeks also resulted in enhanced eosinophil numbers in the BAL fluid and lung tissue, as well as increased goblet cell counts in the airway epithelium following exposure to OVA aerosol relative to air exposure plus OVA aerosol alone (Miyabara et al., 1998). Diesel exhaust exposure also increased the production of OVA-specific IgE and IgG1, measured in the serum, and the expression of IL-5 in lung tissue. The same investigators evaluated longer term (40-week) exposures to diesel exhaust at 0.3, 1.0, or 3.0 mg/m^3 in OVA-sensitized ICR mice to study the effects on allergen-related airway inflammation (Takano et al., 1998). As in the earlier study, diesel exhaust inhalation exposure enhanced eosinophil recruitment and airway

hyperresponsiveness in mice following challenge with OVA. DE exposure caused a dose-dependent increase in the cellularity of the BAL fluid, including increases in macrophages and neutrophils compared to the clean-air controls. Eosinophilic infiltration into the airways was observed with OVA challenge in the DE exposed mice but not the clean-air controls. DE inhalation also produced a dose-dependent increase in IL-5 in the BAL and lung tissue supernatants, and of GM-CSF in lung tissue supernatants.

Other investigators have evaluated inhalation of diesel exhaust or instillation of DEPM and production of asthma-like symptoms or allergic responses in animal models. Sagai et al (1996) instilled 0.1-0.2 mg DEPM intratracheally to ICR and W/W^{-} mice once per week for 5, 8, 11, or 16 weeks. Controls received buffered saline or 0.2 mg activated charcoal. Bronchoalveolar lavage fluid obtained at sacrifice was centrifuged and differential cell counts conducted on the pellet. Lung tissue was examined for eosinophils and neutrophils. Airway hyperresponsiveness in response to acetylcholine was assessed in some of the mice. Proliferation of mucus cells, mucus secretion into the bronchioles, and edematous changes in the submucosa were observed after 11 or more instillations. In addition, hyperplasia of goblet cells and thickening of the bronchiolar wall were noted. Neutrophils, eosinophils, and lymphocyte infiltration into the lamina propria of the bronchi and bronchioles and accumulation of eosinophils in the bronchi, bronchioles and alveoli were evident ($p < 0.05$ to $p < 0.001$). Eosinophils reached maximal levels at the 11th week and remained elevated thereafter. Degranulation of eosinophils was also observed by transmission electron microscopy. Sialic acid (an indicator of mucus hypersecretion), and the numbers of neutrophils and eosinophils were significantly elevated in the BAL fluid of the 0.2 mg treatment group relative to controls or charcoal-treated animals ($p < 0.05$ to 0.001). Airway hyperresponsiveness in response to acetylcholine challenge was enhanced in a dose-dependent fashion by intra-tracheal instillation of DEPM. In mice instilled with 0.2 mg DEPM, airway resistance increased with only 10% of the acetylcholine required to induce a response in the control animals ($p < 0.001$). These changes were suppressed when superoxide dismutase bound to polyethylene particles was instilled, indicating a role of reactive oxygen species in the airway inflammatory response and the etiology of hyperresponsiveness.

Kobayashi et al. (1997) used a guinea pig model of rhinitis to evaluate the effects of inhaled diesel exhaust on nasal mucosal hyperresponsiveness to histamine. Guinea pigs were exposed either to air or diesel exhaust (1 or 3.2 mg DEPM/m^3), and intranasal pressure, nasal secretion and sneezing in response to histamine dripped into the nostril were measured. Effects of DEPM or carbon particles on sneezing were also assessed following intranasal instillation. DEPM instilled intranasally increased the frequency of histamine-induced sneezing compared to saline administration ($p < 0.05$), but carbon particles did not. Diesel exhaust inhalation at the higher dose increased histamine-induced sneezing three-fold over air exposed controls ($p < 0.05$), and induced nasal secretion significantly ($p < 0.05$). Intranasal pressure was not significantly different after inhalation exposure to diesel exhaust in this study. This study demonstrates that intranasally instilled DEPM and short-term high inhalation exposures to diesel exhaust can aggravate nasal rhinitis in an animal model.

Kobayashi (2000) demonstrated that longer-term inhalation exposure to diesel exhaust (0.3 or 1 mg DEPM/m^3 for five weeks), with intranasal instillation of ovalbumin (OVA) once per week, augmented the sneezing response to OVA challenge and increased the production of anti-OVA IgG and IgE.

Sneezes were counted for 20 minutes after each OVA administration. By the 3rd week, the high dose DE-exposed animals showed increased sneezing in response to OVA challenge relative to controls, and the response increased in the 4th to 6th weeks. By the 4th administration the low-dose group showed an augmented response ($p < 0.05$), which increased in significance in the following weeks. DE exposure increased the titers of anti-OVA IgG and IgE in the systemic circulation several-fold relative to air-exposed controls. DE exposure also increased the number of eosinophils in the nasal epithelium and submucosa, a hallmark of nasal allergic reaction. These studies show enhancement of allergic reactions by diesel exhaust in animal models and support the human studies indicating the same.

b) Developmental and Reproductive Effects

Developmental toxicity as a result of maternal exposure to diesel exhaust has been reported (Watanabe and Kurita, 2001). The anogenital distance was significantly longer in both male and female fetuses following exposure to diesel exhaust from gestation days 7 to 20. This endpoint is indicative of developmental toxicity on the reproductive tract. Developmental toxicity is one of the endpoints of concern for children's health, as noted in the Introduction Section II.B.1. Although exposure resulted in some changes in maternal hormone levels relative to controls, the authors concluded that the effects observed were the result of exposure-induced changes in the fetus and its interaction with the maternal endocrine system, rather than maternal toxicity or adaptation.

Taneda et al. (2000) report anti-estrogenic activity of diesel particle extracts in a model yeast system. In a study by Meek (1998), diesel particle extracts activated the aryl hydrocarbon receptor (as does dioxin) and induced transcription of reporter genes regulated by the AhR and estrogen receptors. These two studies indicate potential endocrine disruption activity by chemicals bound to diesel exhaust particles. Endocrine disruption is noted in the introduction as a toxicological endpoint of concern for children.

The summary of PAH effects in this report lists extensive developmental effects of PAH exposure, including teratogenesis. It is plausible that such effects would result also from exposure to diesel exhaust due to its PAH content. However, it does not appear that the endpoints observed for PAH developmental toxicity have been adequately evaluated for diesel exhaust exposure.

V. Additional Information

A. Mutagenicity

Diesel exhaust particles have been shown to be mutagenic in a variety of assays *in vitro*, including the *Salmonella* reverse mutation assay and various assays in mammalian cells. Induction of chromosome aberrations *in vitro*, and of sister chromatid exchanges and micronuclei both *in vitro* and *in vivo*, has also been observed. Formation of DNA adducts, in some cases identified as derived from PAHs and/or nitro-PAHs, has been reported both *in vivo* and *in vitro*. Genetic toxicity of diesel exhaust and of particulate material derived therefrom was reviewed in detail by OEHHA (1998). Note that levels of PAH-DNA adducts have been associated with low birth weight in humans (see PAH summary).

B. Regulatory Background

Diesel exhaust PM is listed as a toxic air contaminant under California's air toxics program (AB 1807). OEHHA (1998) reported the following cancer potency estimates:

Unit Risk Factor: 1.3 E-4 - 1.5 E-3 $(\mu g/m^3)^{-1}$ (measured as particulate matter)
[Scientific Review Panel unit risk "reasonable estimate" = 3.0 E-4 $(\mu g/m^3)^{-1}$.]

Slope Factor: 1.1 E+0 $(mg/kg\text{-}day)^{-1}$

This estimate was based on human occupational exposure lung tumor incidence in studies of US railroad workers (Garshick *et al*. (1987, 1988), using estimated exposure concentrations (Woskie *et al*., 1988a,b) and a relative risk model (OEHHA, 1998). Additional analyses by others support this range of risk (Harris, 1983; Steenland et al., 1998).

Diesel exhaust is listed as a carcinogen under Proposition 65, and IARC (1989) lists diesel exhaust as a probable human carcinogen (Group 2A).

OEHHA has adopted a chronic Reference Exposure Level of 5 $\mu g/m^3$. The REL is based primarily on two studies. Ishinishi et al. (1988) showed histological changes in the lung in rats exposed to diesel exhaust at concentrations of 0.96 mg particulate/$m^3$and higher, and Mauderly et al. (1988) showed inflammatory, histological, and biochemical changes in the lung of rats exposed to 3.47 mg diesel exhaust particulate/m^3. The NOAEL, after adjustment for dosimetry used in estimating the REL, was 155 $\mu g/m^3$ for the Ishinishi study; application of a cumulative uncertainty factor of 30 led to an REL of 5 $\mu g/m^3$. Statewide average ambient concentrations are about one-half of the REL, while concentrations can exceed that in urban areas and inside vehicles.

VI. Conclusions

From the above discussion, it is apparent that diesel exhaust has the potential to disproportionately impact infants and children, and OEHHA has, therefore, placed diesel exhaust particulate in Tier 1. The development of atopy, a major risk factor for childhood asthma, occurs as a result of exposures in early childhood among individuals with a genetic predisposition to produce IgE. Enhanced allergic and inflammatory responses have been observed in both animals and humans exposed intranasally or via inhalation to diesel exhaust particulate. Numerous studies indicate that exposure to diesel exhaust particles can:

- Increase total IgE and IgG4 in humans and animals.
- Potentiate responses to allergen, producing marked increases in allergen-specific IgE.
- Favor the activation of Th-2 over Th-1 lymphocytes, enhancing the production of Th2 cytokines, which are associated with allergic inflammation.

- Cause degranulation of eosinophils, with increased release of histamine, and worsen symptoms of allergic rhinitis in humans.
- Cause marked acute airway inflammation in humans after controlled exposures.
- In animal models, cause chronic eosinophilic inflammation and airway hyperreponsiveness, two of the principal characteristics of asthma.
- Facilitate the development of allergy in the presence of diesel exhaust particulate where exposure to the allergen alone was insufficient to induce an allergic response.

Studies of DEPM-associated PAHs suggest plausible mechanisms by which diesel exhaust may exert this suite of immunological effects. The adjuvant effects of diesel exhaust exposure may influence exacerbations of, and perhaps the development of atopic conditions, including allergic rhinitis and asthma. While the precise role (if any) of diesel exposure in the development of atopy has not been defined, evidence has accumulated over the past decade that exposures to a variety of agents that impact the immune system during the first few years of life are critical in determining whether an individual will develop an allergic diathesis.

In addition to the mechanistic evidence from human and animal studies, several studies have shown that exposure to ambient PM_{10} leads to exacerbation of asthma, lung function decrements and increased cough, wheeze, and chronic bronchitis in children. Diesel exhaust is a component of PM_{10}. The extent of the contribution of diesel exhaust particulate to PM_{10} health effects in children and adults has not been directly studied. However, exacerbation of asthma and other adverse health impacts from PM_{10} may, in part, be attributable to DEPM exposure. More to the point, a range of adverse respiratory impacts in children has been associated with traffic density, and especially heavy-duty diesel-fueled truck traffic density and measures of black smoke (sooty fine particles). One of these traffic studies suggests that children are more affected by traffic-related pollutants than adults in the same household. Respiratory impacts may be greater in very young children because their developing lung and immune systems are especially vulnerable to chemical insult. Asthma is potentially more serious in children, especially very young children, because of their smaller airways (see Introduction Section II). Thus, decrements in lung function, exacerbation of asthma and possibly induction of allergic asthma facilitated by diesel exhaust particulate exposure may contribute to disproportionate impacts of diesel exhaust on children.

Epidemiological studies have also provided evidence that exposure to PM_{10} is associated with increased infant mortality. Diesel exhaust is a major contributor to PM_{10} in some of the areas studied (e.g., Bangkok, Mexico, New Delhi), but is not as significant in the U.S. Nonetheless, diesel exhaust particulate contributes to PM_{10} and thus may, in part, be responsible for this observed effect; certainly, there is not a protective effect in the cities where diesel exhaust contributes a substantial portion of the PM_{10}.

Diesel exhaust particulate contains approximately 1% PAHs. Several non-carcinogenic effects have been observed following exposure *in utero* to PAHs or to mixtures containing them, and are described in the PAH summary in this report. These included teratogenesis, low birth weight in humans and

rodents, immunotoxicity, loss of fertility in rodents exposed to benzo[a] pyrene *in utero*, and disruption of lymphocyte maturation and hematopoiesis. These occurred at doses at which maternal toxicity (other than long-term effects such as carcinogenesis) is minimal or absent. In several cases the effects observed after exposure *in utero* parallel toxic effects in the adult (e.g. immunotoxicity, reproductive toxicity, myelotoxicity), but whereas the effects are reversible after exposure of the adult, exposure of the fetus results in an irreversible effect. There are many carcinogenic PAHs and several studies showing that potency increases when exposure occurs perinatally. Thus, the presence of PAHs on diesel exhaust particles is another reason to consider that DEPM disproportionately impacts children.

Children have higher exposures to airborne particles than do adults at the same particle concentration due to their higher breathing rates (see Introduction Section III.). In addition, higher particle doses are experienced by children per unit of alveolar surface area due to particle deposition dynamics. Thus, exposures to diesel exhaust particles in the same environmental settings may be greater for children than for adults.

With regard to diesel exhaust carcinogenesis, the evidence indicating that infants and children may be more susceptible than adults is mainly indirect, since studies of this endpoint in children are not available. However, the more extensive data on PAHs and carcinogenesis reported in the summary for PAHs tend to support the expectation that higher risk might be incurred by exposure to diesel exhaust as infants and children than adults.

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